[2] Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;i:1261-7.
[3] Stamler J, Farinaro E, Mojonnier LM, Hall Y, Moss D, Stamler R. Prevention and control of hypertension by nutritional-hygienic means. *JAMA* 1980;**243**:1819-23.
[4] Anonymous. Lowering blood pressure without drugs. *Lancet* 1980;ii: 459-61.
[5] Patel C. Yoga and biofeedback in the management of hypertension. *Lancet* 1973;ii:1053-5.
[6] Patel C. 12-month follow-up of yoga and biofeedback in the management of hypertension. *Lancet* 1975;i:62-4.
[7] Patel C, North WR. Randomized controlled trial of yoga and biofeedback in the management of hypertension. *Lancet* 1975;ii:93-5.
[8] Datey K, Deshmukh SN, Dalvi CP, Vinekar MD. "Shavasan"; a yogic exercise in the management of hypertension. *Angiology* 1969;**20**:325-33.
[9] Benson H, Shapiro D, Tursky B, Schwartz G. Decreased systolic blood pressure through operant conditioning techniques in patients with essential hypertension. *Science* 1971;**173**:740-2.
[10] Elder ST, Ruiz ZR, Deabler HL, Dillenkoffer RL. Instrumental conditioning of diastolic blood pressure in essential hypertensive patients. *J Appl Behav Anal* 1973;**6**:377-82.
[11] Kristt DA, Engel BT. Learned control of blood pressure in patients with high blood pressure. *Circulation* 1975;**51**:370-8.
[12] Benson HB, Rosner BA, Marzetta BR, Klemchuk HM. Decreased blood pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. *Lancet* 1974;i:289-91.
[13] Shoemaker JE, Tasto DL. The effects of muscle relaxation on blood pressure in essential hypertensives. *Behav Res Ther* 1975;**13**:29-43.
[14] Blackwell BS, Bloomfield P, Grantside P, *et al.* Transcendental meditation in hypertension. *Lancet* 1976;i:223-6.
[15] Stone A, De Leo J. Psychotherapeutic control of hypertension. *N Engl J Med* 1976;**294**:80-4.
[16] Deabbler HL, Fedel E, Dillenkoffer RL. The use of relaxation and hypnosis in lowering high blood pressure. *Am J Clin Hypn* 1973;**16**: 75-83.
[17] Taylor CB, Farquar JW, Nelson E, Agros S. Relaxation therapy and high blood pressure. *Arch Gen Psychiatry* 1977;**34**:339-42.
[18] Peters RK, Benson H, Peters JM. Daily relaxation response breaks in a working population. II. Effects on blood pressure. *Am J Public Health* 1977;**67**:954-9.
[19] Luborsky L, Crits-Christoph P, Brady JP, Kron RE, Weiss T, Engelman K. Antihypertensive effects of behavioral treatments and medications compared. *N Engl J Med* 1980;**303**:586.
[20] Rose GA. Standardisation of observers in blood pressure measurement. *Lancet* 1965;i:673-4.
[21] Oparil S, Katholi R. Renin release—autonomic mechanisms. In: Oparil S, Katholi R, eds. *Renin.* Vol 3. Edinburgh: Churchill Livingstone, 1978: 35-73.
[22] Folkow B, Hallback M. Lundgren Y, Sivertsson R, Weiss L. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. *Circ Res* 1973;**32**, suppl 1:2-16.
[23] Vaughan Williams EM, Hassan MO, Floras JS, Sleight P, Jones VJ. Adaptation of hypertensives to treatment with cardio selective and non-selective beta-blockers. Absence of correlation between bradycardia and blood pressure control and reduction in slope of QT/RR relation. *Br Heart J* 1980;**44**:437-97.

(*Accepted 22 April 1981*)

Aquagenic pruritus

M W GREAVES, A K BLACK, R A J EADY, A COUTTS

Abstract

Three patients were studied in whom brief contact of the skin with water at any temperature evoked intense itching without visible changes in the skin. The patients were otherwise apparently healthy, and this chronic and disabling disorder tended to attract a "psychogenic" label. Pharmacological studies showed that the condition was associated with local release of acetyl choline in the skin, mast-cell degranulation, and raised blood histamine concentrations. It responded well to antihistamines in two of the three patients.

Aquagenic pruritus is probably common, but it is generally unrecognised and may be misdiagnosed. Antihistamines may induce a good therapeutic response.

Introduction

Transitory contact of the skin with water is generally thought to be completely innocuous. This report describes a novel and disabling reaction of the skin to water with mast-cell degranulation and increased circulating histamine activity. Its recognition is important because sufferers are liable to be labelled "neurotic" and because it responds well to antihistamines. It also appears to be a common disorder.

Institute of Dermatology, St John's Hospital for Diseases of the Skin, London E9
M W GREAVES, MD, FRCP, professor of dermatology
A K BLACK, MRCP, senior lecturer and consultant
R A J EADY, MRCP, senior lecturer and consultant
A COUTTS, PHD, lecturer

Case reports

CASE 1

A 24-year-old Ghanaian catering student who had been living in Britain for nine years complained of intense extensive pruritus after contact of her skin with water at any temperature. The complaint had been present persistently for 14 years and there were no visible skin changes. Typically, the irritation developed on the legs within a few minutes of immersion in a hot or cold bath, became generalised, and lasted 15-45 minutes. It was associated with dizziness and palpitations. Of the several doctors who had seen her previously, one had considered that she had "a number of personality problems" and another that she had a "psychogenic problem." Exposure to cold, heat, exercise, and emotional stimuli produced no effects. General medical history and examination contributed nothing. The skin looked normal and she was not dermographic. Exercise on a stationary bicycle failed to reproduce the symptoms. Laboratory tests including full blood variables, thyroid function, liver and renal function, serum IgE concentration, and serum complement components were all within normal limits.

She was immersed in water at 37°C for 15 minutes up to her upper chest. After four minutes she developed intense itching in the front and back of the legs. After 15 minutes this had spread to the back, but at 35 minutes it had diminished considerably. There were no visible skin changes. She had no systemic symptoms on this occasion, and peak expiratory flow rate measured by Wright's peak flow meter was 440 l/min before immersion and varied from 430 to 460 l/min after immersion. An area of skin in which sweating had been blocked by earlier topical application of 3% hyoscine solution failed to itch, although surrounding skin itched. Cimetidine 200 mg and chlorpheniramine 8 mg were both given six hourly for 24 hours. Immersion in

water as described above produced little or no itching. After withdrawal of this treatment for 48 hours the symptoms recurred as before. Subsequently she found that treatment with chlorpheniramine 8 mg two hours before bathing controlled her symptoms satisfactorily.

CASE 2

For seven and a half months a 31-year-old male Iraqi physics student had suffered severe itching that started one minute after contact with water at any temperature. He said that he had been told he was "neurotic" by several doctors. The itching, which lasted 15-35 minutes and affected mainly the thighs and arms, was not associated with any visible skin abnormality. There were no systemic symptoms. Exposure to cold, heat, exercise, and emotional stimuli did not cause any untoward symptoms. General medical history and examination yielded no abnormality. There was no dermatographia, and the skin looked normal. Exercise on a stationary bicycle did not reproduce the symptoms. Laboratory investigations including blood variables were normal. Exposure to a warm shower produced intense itching of the thighs and arms without visible skin changes, but immersion to the neck in water at 37°C for 15 minutes failed to reproduce the symptoms. He was treated with ketotifen 1-2 mg one to two hours before bathing, but this failed to relieve his symptoms.

CASE 3

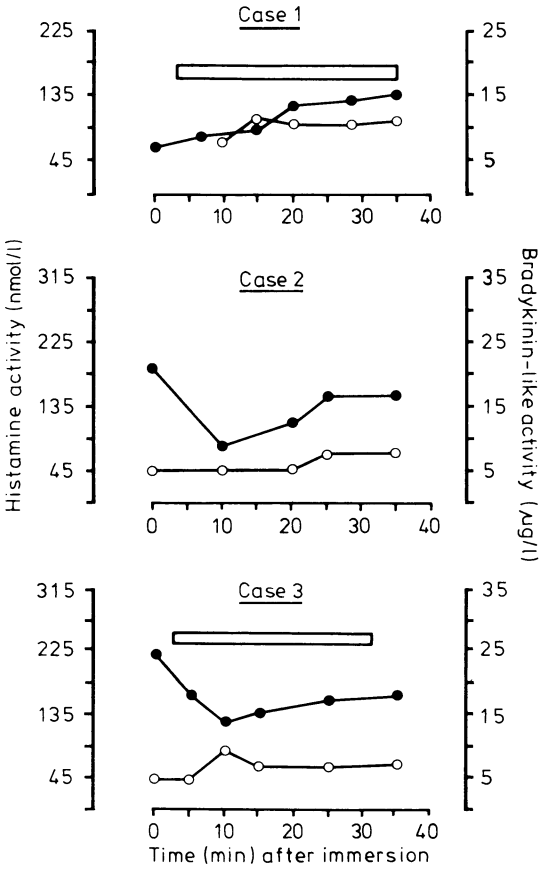
For two years a 40-year-old Caucasian housewife had suffered severe itching and burning on the thighs and lower legs after contact with water during a bath or shower at any temperature. The affected skin looked normal during these attacks. The irritation began on the outer surface of the thighs two minutes after exposure to water and spread to the lower legs, sparing the feet. It lasted three to 120 minutes, and there were no systemic symptoms. Exposure to cold, heat, exercise, and emotional stimuli did not reproduce the attacks. General medical history and examination were unhelpful, the skin looked normal, and tests for dermatographia were negative. Exercise on a stationary bicycle produced no symptoms. Laboratory tests including blood variables were normal. Peak expiratory flow rate was 370-390 l/min.

She was immersed in water at 37°C for 15 minutes up to her upper chest. Three minutes after immersion she complained of itching of the back of the calves. Four minutes after immersion the peak expiratory flow rate was 400 l/min. By five to nine minutes itching had spread to the thighs and inguinal areas and the peak expiratory flow rate was 420 l/min. There were no systemic symptoms, and the skin looked normal throughout. At 30 minutes the itching had subsided. Blockade of sweating by topical pretreatment of a circumscribed area of thigh skin with 3% hyoscine solution inhibited sweating and itching, although a symmetrical untreated area on the contralateral limb itched profusely after exposure to water. The next day repeat immersion in water at 42°C but otherwise as described above produced itching limited to the calves. Chlorpheniramine 8 mg and cimetidine 200 mg, both given six hourly for 24 hours, completely prevented itching due to contact with water. Subsequent follow-up showed that treatment with cimetidine 400 mg three times a day and chlorpheniramine 4 mg each morning completely suppressed the itching, although if she omitted this regimen the symptoms recurred acutely. Chlorpheniramine alone proved ineffective.

Pharmacological studies

Blood samples were obtained from the antecubital vein using an indwelling cannula before and at regular intervals after immersion in water at 37°C up to the upper chest or neck for 15 minutes. Pharmacological activity was detected and measured by the cascade superfusion bioassay technique of Vane.[1] Two preparations were made from adjacent segments of guinea-pig ileum, and preparations of the rat stomach fundus strip and rat duodenum were also set up. The preparations were mounted under 0·4 g tension in separate organ jackets arranged vertically in series. The preparations were superfused by Krebs solution containing atropine (10^{-6} mol/l; 0·29 mg/l), indomethacin ($2{\cdot}8\times10^{-6}$ mol/l; 1·0 mg/l), methysergide ($4{\cdot}3\times10^{-7}$ mol/l; 0·15 mg/l), and mepyramine ($2{\cdot}5\times10^{-7}$ mol/l; 0·07 mg/l), although mepyramine was omitted from the superfusate bathing the first ileum preparation. Contractions of all preparations were recorded isometrically on a Devices heat-pen recorder.

Biological activity in the blood samples was compared with that due to an equal volume of several standard drug solutions dissolved in Krebs solution. The volume of blood or standards added to the superfusate was 300 μl, and additions were made during continuous flow. The standard solutions used were histamine acid phosphate, bradykinin, prostaglandin E_2, and prostaglandin $F_{2\alpha}$. There was no detectable prostaglandin activity in any of the samples from the three subjects. Erythema, weal, and sensory responses to intradermal injections of bradykinin 0·1-1·0 μg, histamine 0·5-5·0 μg, and prostaglandin E_2 0·01-0·1 μg in phosphate-buffered saline diluent in the thighs were within normal limits in the two patients tested (cases 2 and 3).



Histamine activity (●——●) and bradykinin-like activity (○——○) in the three patients. Horizontal bars indicate onset and duration of itching, which did not occur in case 2 in the experiment. (Upper limit of normal for venous blood histamine concentrations in control subjects after whole-body immersion in water at 44°C for 15 minutes in this laboratory is 41·4 nmol/l (4·6 ng/ml).)

Conversion: SI to traditional units—Histamine: 1 nmol/l ≈0·11 ng/ml.

If the response on the first ileum preparation was blocked by mepyramine on the second, this activity was considered to be due to histamine. The amount of histamine in the blood samples was estimated by bracketing the response to the unknown samples between greater and lesser responses to standard solutions of histamine. Bradykinin-like activity was estimated by comparing the relaxation of the rat duodenum preparation with that to standard bradykinin solutions in order to bracket the unknown sample. The figure summarises the results.

CASE 1

The venous blood histamine concentration was 54 nmol/l (6 ng/ml) before bathing, rising progressively to 126 nmol/l (14 ng/ml) after immersion. During this period the patient experienced intense pruritus. Bradykinin-like activity was not measured before bathing but remained fairly constant at 7·5-10 μg/l during the period of observation.

CASE 2

The control blood histamine concentration (before immersion) was high (189 nmol/l; 21 ng/ml), and, although the concentration fell during the initial 10 minutes after immersion, it increased progressively during the remainder of the experiment. Bradykinin-like activity ranged from 5 to 7·4 μg/l throughout. Unexpectedly, the patient experienced no itching during this experiment.

CASE 3

This patient also had an unusually high control blood histamine concentration, which declined after immersion but subsequently rose slightly during the period of itching. In this period, as in the previous two cases, blood histamine concentrations were consistently higher than control values in healthy subjects subjected to whole-body immersion at 45°C for 15 minutes (< 45 nmol/l; 5 ng/ml). Bradykinin concentrations remained fairly constant at 5-7·5 μg/l.

Morphological studies

Skin biopsy specimens (4 mm in diameter) were taken from the ventral aspect of the thighs of the three subjects before and 15 minutes after immersion for 15 minutes in a bath containing tap water at 37°C. Lignocaine 1% (without adrenaline) was injected intradermally as a local anaesthetic. Each biopsy specimen was divided and processed for estimation of mast-cell population density[2] and mast-cell degranulation. Mast-cell degranulation was assessed by light microscopical examination of 1-μm thick Epon sections stained with basic fuchsin and methylene blue or with Giemsa stain. Degranulation was deemed to have occurred when free granules could be identified surrounding a mast cell. Both mast-cell counts and estimates of degranulation were done blind, the investigator having no knowledge of the experimental circumstances of the material he was studying.

The table shows the mast-cell population density and percentage degranulation. The values are the means derived from counts in two subsamples (blocks) from each biopsy. Mast-cell numbers in unchallenged skin from the patients did not differ significantly from those reported in healthy skin of normal subjects. The numbers of mast cells in thigh skin of the patients before and after immersion were also not significantly different. The percentage degranulation in the patients' skin before challenge, however, was significantly greater than that in healthy skin of normal subjects ($t = 2{\cdot}80$, $p < 0{\cdot}025$, $df = 5$; unpaired t test). Moreover, the percentage degranulation was significantly increased after challenge by ($t = 3{\cdot}96$, $p < 0{\cdot}05$, $df = 2$; paired t test). In one patient (case 3) mast cells in a biopsy specimen obtained after challenge were examined by electron microscopy. Ultrathin sections were stained with uranyl acetate and lead citrate. Degranulation of several dermal mast cells was confirmed. The changes observed on light microscopy were confirmed. In addition, intracellular changes consistent with exocytosis as described in rat peritoneal mast cells undergoing histamine secretion were also noted.[3]

Numbers of skin mast cells and percentage degranulation before and after immersion in water at 37°C (figures in parentheses are total numbers of mast cells examined per patient (from thigh))*

Case No	Before challenge		After challenge	
	Mast cells/mm²	% Degranulation	Mast cells/mm²	% Degranulation
1	45·65	32·95 (123)	29·2	40·12 (103)
2	83·3	24·73 (443)	61·43	25·16 (405)
3	44·04	13·1 (273)	56·77	25·77 (239)

*Normal ranges for forearm: 34·8-66·4 mast cells/mm² (ref 2) and 10·15-13·5% degranulation (unpublished data).

Discussion

Aquagenic pruritus must be distinguished from other causes of irritant reactions in response to the contact of water with the skin, including cold urticaria, provoked by contact with cold water; cholinergic urticaria, associated with sweating; and symptomatic dermatographia, which is often provoked by towelling after a bath or by jets of water during showering. The condition presents important differences as well as similarities with the rare aquagenic urticaria.[4] Patients with aquagenic pruritus have no urticaria lesions. Patients with aquagenic urticaria, however, present with a striking monomorphic eruption consisting of pin-head weals and surrounding erythematous flares at the site of water contact. These lesions often become confluent and are extremely itchy. Unlike aquagenic pruritus, which invariably appears on the legs, although it may spread elsewhere, aquagenic urticaria is normally confined to the upper part of the body. Both aquagenic urticaria and aquagenic pruritus, however, are inhibited by topical application of hyoscine, and in both histamine is released, implying that release of acetyl choline and mast-cell degranulation are involved in both disorders.[5] The pruritus induced by contact with water in patients with polycythaemia vera resembles that occurring in our patients and, interestingly, is also associated with raised blood histamine concentrations without accompanying visible skin changes in most patients.[6]

All three patients with aquagenic pruritus had raised blood histamine concentrations, which in two were abnormally high even before immersion in water. Although mast-cell numbers in thigh skin appear to be normal in patients with aquagenic pruritus, the condition is associated with an abnormally high percentage of degranulated skin mast cells before challenge with water, which increases still further after challenge. The cause of the high blood histamine concentrations and the high proportion of degranulated mast cells before challenge is not clear, but these changes might be a result of sweating. Despite the greatly increased blood histamine concentrations in all three patients after immersion systemic symptoms occurred in only one (case 1) and none had an impaired peak expiratory flow rate.

The pathogenesis of aquagenic pruritus requires detailed study. Hydration of the stratum corneum may result in percutaneous absorption of a factor in or on the stratum corneum. Subsequent steps appear to include secretion of acetyl choline and release of histamine from mast cells. That no visible changes occur in the skin despite clear evidence of histamine release is surprising. The rate of release of histamine in the skin may be slow, however, despite the visible appearances of fairly extensive mast-cell degranulation.

We have not found any previous reports of patients with aquagenic pruritus, although some doctors are aware of its existence.[7] That the condition is common is suggested by the number of our colleagues who now recollect having seen patients with identical symptoms in the past, sometimes labelled as "psychogenic." Recognition of the condition is important because it responded well to treatment with an H_1-antihistamine with or without an H_2-antihistamine in two of our patients; in the third (case 2) reponse to antihistamines was incompletely studied.

We thank Andrew Kennedy for technical help with mast-cell counts. The work was supported by the Medical Research Council and the Herbert E Dunhill Trust.

References

1 Vane JR. The use of isolated organs for detecting active substances in the circulating blood. *Br J Pharmacol* 1964;**23**:360-6.
2 Eady RAJ, Cowen T, Marshall TF, Plummer V, Greaves MW. Mast cell population density, blood vessel density and histamine content in normal human skin. *Br J Dermatol* 1979;**100**:623-33.
3 Uvnas B. Histamine storage and release. *Fed Proc* 1974;**33**:2172-6.
4 Shelley WB, Rawnsley HM. Aquagenic urticaria; contact sensitivity reaction to water. *JAMA* 1964;**189**:895-8.
5 Sibbald RG, Black AK, Eady RAJ, James M, Greaves MW. Aquagenic urticaria; evidence of cholinergic and histaminergic basis. *Br J Dermatol* (in press).
6 Gilbert HS, Warner RP, Wasserman LR. A study of histamine in myeloproliferative disease. *Blood* 1966;**28**:795-806.
7 Shelley WB. Questions and answers. *JAMA* 1970;**212**:1385.

(*Accepted 21 April 1981*)